PRECURSOR CELLS IN SKELETAL MUSCLE REPAIR AND HYPERTROPHY

RELEASE DATE: July 25, 2002

PA NUMBER: PA-02-136

EXPIRATION DATE: March 30, 2006

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(http://www.niams.nih.gov/)

National Institute on Aging (NIA)
(http://www.nia.nih.gov)

National Institute of Child Health and Human Development (NICHD)
(http://www.nichd.nih.gov/)

National Institute of Neurological Disorders and Stroke (NINDS)
(http://www.ninds.nih.gov)

THIS PA CONTAINS THE FOLLOWING INFORMATION

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological Disorders and Stroke (NINDS) encourage investigator-initiated research grant applications to isolate, characterize and identify precursor cells required for normal growth and repair of injured, aged, or diseased muscle. Goals include determining factors responsible for migration, proliferation, and differentiation of precursor cells following muscle injury or increased exercise. This includes characterizing molecular controls responsible for the quiescence of muscle satellite cells and determining metabolic and motile properties of satellite cells while they are quiescent. Researchers are encouraged to develop strategies using muscle satellite and stem cells in therapies for human disease and enhanced repair of muscle injury and as cellular vectors of genes.

RESEARCH OBJECTIVES

Background

Mammalian muscle contains a set of cells capable of regeneration and repair. These regenerative cells play an important role in the considerable growth of post natal muscle, with skeletal muscle representing 40-50 % of the weight of adults. An important question in muscle development and muscle repair is the origin of these cells and their relationship to stem cells that circulate within the blood.

Normal repair and exercise induced cellular hypertrophy of skeletal muscle is mediated by quiescent, undifferentiated cells. These are called satellite cells because of their anatomic location, within the basal lamina at the periphery of mature skeletal muscle fibers. Following muscle injuries, or in response to increasing work demands, satellite cells are mobilized to proliferate, differentiate, and fuse into multinucleate myofibers. Little is known about the developmental origins of satellite cells or the mechanisms that restrict differentiation and maintain their quiescence while associated within functioning muscles. Similarly, there is little characterization of the molecular steps which occur in the recruitment of satellite cells for repair from injury or disease. In addition, little is understood about possible changes in potential for differentiation or population dynamics of satellite cells with aging that may be important to loss of muscle mass in the elderly.

Recent research showed the existence of a small population of muscle-derived stem cells that are multipotent, which can contribute to the formation of blood and bone tissue as well as muscle. Additionally, muscle that is repairing itself can recruit circulating non-muscle stem cells and

convert them into myogenic precursors. Knowledge of how such cells function in muscle growth is limited.

Scope and Objectives

This initiative encourages research on cells involved in skeletal muscle growth and repair. Goals include determining factors responsible for migration, proliferation, and differentiation of precursor cells following muscle injury or increased exercise. This includes characterizing molecular controls responsible for the quiescence of muscle satellite cells and determining metabolic and motile properties of satellite cells while they are quiescent.

Researchers are encouraged to develop strategies using muscle satellite and stem cells in therapies for human disease and enhanced repair of muscle injury and as cellular vectors of genes. One such aim is to develop methods that enhance repair of muscle injuries with minimal fibrosis and scarring.

Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients. Investigators with diverse scientific interests are invited to apply their expertise to basic, applied, and clinical research to enhance understanding precursor cells involved in skeletal muscle growth and repair. Examples that illustrate possible areas of research are presented below. They are intended only to provide a broad direction for research and should be considered illustrative and not restrictive.

o Projects to identify, isolate, culture and characterize cells that are precursors of muscle growth or regeneration.

o Projects to generate and use panels of markers for use in characterization and isolation of skeletal muscle precursor cells.

o Studies to determine the origins and fates of muscle precursor cells.

o Characterization of differences between skeletal muscle cells and other muscle precursor cells derived from muscle.

o Research on mechanisms governing the role of muscle precursor cells in muscle plasticity and adaptation and aging.

o Research to characterize molecular controls responsible for the quiescence of muscle satellite cells and determining metabolic and motile properties of satellite cells while they are quiescent, including quiescent satellite cells in aged muscle.

o Characterization of biological functions of muscle precursor cells.

o Research to develop and optimize methodologies for expanding the differentiation of muscle precursor cell populations, or understanding if precursor populations from aged muscle have altered requirements for differentiation.

o Projects to create methods of culture to maintain muscle precursor cells in stages when they proliferate.

o Studies to elucidate mechanisms of muscle precursor cell differentiation

o Research to develop and optimize methodologies for directing the differentiation of muscle precursor cell populations.

o Research to minimize inappropriate differentiation during the repair process that leads to fibrosis (contractures) or calcification (myositis ossificans, fibrodysplasia ossificans progressiva.)

o Applying muscle precursor cell therapies to muscle diseases and disuse muscle atrophy or wasting (also called sarcopenia).

o Research to develop strategies using muscle satellite and stem cells in therapies for human disease and enhanced repair of muscle injury and as cellular vectors of genes.

o Use of precursor cells in the context of exercise, functional electrical stimulation (FES) or other therapeutic strategies.

MECHANISM OF SUPPORT

This PA will use the NIH individual research project grant (R01) award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications.

Investigators should contact program staff listed under INQUIRIES to discuss applications using other mechanisms, such as the program project grant.

ELIGIBLE INSTITUTIONS

You may submit an application if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic or foreign

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research and financial or grants management issues:

Direct your questions about scientific/research issues to:

Richard W. Lymn, Ph.D.
Muscle Biology Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza

6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5128
FAX: (301) 480-4543
Email: LymnR@mail.nih.gov

Jill L. Carrington, Ph.D.
Musculoskeletal Biology
Biology of Aging Program
National Institute on Aging
7201 Wisconsin Avenue Suite 2C231
Bethesda, MD 20892
Telephone: (301) 496-6402
FAX: (301) 402-0010
Email: carringtonj@nia.nih.gov

Ralph M. Nitkin, Ph.D.
National Center for Medical Rehabilitation Research
National Institute of Child Health and Human Development
Building 6100E/Room 2A03
6100 Executive Blvd MSC 7510
Bethesda, MD 20892-7510
Email: rn21e@nih.gov

Giovanna M. Spinella, M.D.
Neurogenetics and Development
National Institute of Neurological Disorders and Stroke
6001 Executive Blvd. Rm. 2132
Rockville, MD 20892-9527
Telephone: (301) 496-5745
FAX: (301) 401-1501
Email: gs41b@nih.gov

o Direct your questions about financial or grants management matters to:

Melinda Nelson
Grants Management Officer

National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd. Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: nelsonm@mail.nih.gov

Linda Whipp
Grants and Contracts Management Office
National Institute on Aging
7201 Wisconsin Avenue, Suite 2N212, MSC 9205
Bethesda, MD 20892-9205
Telephone: (301) 496-1472
FAX: (301) 402-3672
Email: whippl@nih.gov

Christopher Myers
Grants Management
National Institute of Child Health and Human Development
Building 6100E/Room 8A17
6100 Executive Blvd MSC 7510
Bethesda, MD 20892-7510
Email: cm143g@nih.gov

Sheila Simmons
Grants Management Officer
National Institute of Neurological Disorders and Stroke
6001 Executive Blvd. Rm. 3250
Rockville, MD 20892
Telephone: (301) 496-9231
FAX: (301) 402-0219
Email: simmonss@ninds.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING $500,000 OR MORE PER YEAR: Applications requesting $500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application.

Applicants requesting more than $500,000 must carry out the following steps:

1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received by or mailed on or before the receipt dates described at http://grants.nih.gov/grants/funding/submissionschedule.htm. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

o Receive a written critique
o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

o Significance
o Approach
o Innovation
o Investigator
o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

(3) INNOVATION: Does your project employ novel concepts, approaches or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies?

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below)

DATA SHARING: The adequacy of the proposed plan to share data.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

o Scientific merit of the proposed project as determined by peer review
o Availability of funds
o Relevance to program priorities

REQUIRED FEDERAL CITATIONS

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In

addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html);
a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.
The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance Nos. 93.846, 93.866, 93.929 and 93.853 and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at http://grants.nih.gov/grants/policy/policy.htm and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index
Return to NIH Guide Main Index